Guidance for Industry
Carcinogenicity Study Protocol Submissions

DRAFT GUIDANCE

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For questions regarding this draft document contact Joseph DeGeorge 301-594-5476.

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Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance/index.htm

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If you plan to submit comments on this draft guidance, to expedite FDA review of your comments, please:

- *Clearly explain each issue/concern and, when appropriate, include a proposed revision and the rationale/justification for the proposed change.*
- *Identify specific comments by line number(s); use the PDF version of the document, whenever possible.*

I. INTRODUCTION

This guidance is intended to inform sponsors of the types of information the Center for Drug Evaluation and Research (CDER) relies on when evaluating protocols for animal carcinogenicity studies.

II. BACKGROUND

The Prescription Drug User Fee Act of 1992 (PDUFA) was reauthorized in the Food and Drug Administration Modernization Action of 1997. In conjunction with the reauthorization of PDUFA, FDA agreed to specific performance goals (PDUFA goals) for activities associated with the development and review of products in human drug applications.[2] The PDUFA goals are summarized in *PDUFA Reauthorization Performance Goals and Procedures*, an enclosure to a letter dated November 12, 1997, from the Secretary of Health and Human Services, Donna E. Shalala, to Senator James M. Jeffords.

The PDUFA goals related to special protocol assessment and agreement provide that, upon request, FDA will evaluate within 45 days certain protocols and issues relating to

[1] This guidance has been prepared by the Office of Review Management in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

[2] The term *human drug applications* is defined in section 735(1) of the Federal Food, Drug, and Cosmetic Act.

the protocols to assess whether or not they are adequate to meet scientific and regulatory requirements identified by the sponsor. Protocols for animal carcinogenicity studies are eligible for this special protocol assessment.[3] This guidance is intended to facilitate the Agency's review of protocols for animal carcinogenicity studies by informing sponsors of the types of information the Agency relies on during its evaluation of such protocols.

Although protocol submissions not supplying all of the information described in this document may be evaluated by CDER, an incomplete package may make it extremely difficult for the Agency to reach agreement on a protocol or recommend alternative study designs within the 45-day time frame described in the PDUFA goals.

Prior to designing carcinogenicity studies, sponsors should review the ICH guidances *S1C Dose Selection for Carcinogenicity Studies of Pharmaceuticals* (March 1995) and *S1C(R) Guidance on Dose Selection for Carcinogenicity Studies of Pharmaceuticals: Addendum on a Limit Dose and Related Notes* (December 1997). The highest dose to be included in a carcinogenicity study should be based on one of the ICH endpoints.[4] Sponsors also should review *S1B Testing for Carcinogenicity of Pharmaceuticals* (February 1998), which provides guidance on species selection and alternative approaches to the standard 2-species/2-year testing paradigm.

III. GUIDANCE ON PROTOCOL SUBMISSIONS

In CDER, primary responsibility for the review of protocols for animal carcinogenicity studies lies with the review division. The review division consults with CDER's Carcinogenicity Assessment Committee (CAC) or CDER's Executive Carcinogenicity Assessment Committee (Exec CAC). These committees provide a tertiary review of the study protocols and provide written comments on the appropriateness of the protocol from CDER's perspective on approaches to testing, including the study type, doses employed, and other design issues.

To facilitate the review process, sponsors should notify the Agency in writing that a carcinogenicity protocol will be arriving at least 30 days prior to submission of the study protocol. The carcinogenicity protocol and questions regarding the protocol should be submitted in sufficient time prior to the anticipated initiation of the study to allow for meaningful discourse with the Agency and resolution of any issues before study initiation. Submission should be made to the appropriate review division in CDER. The submission should be clearly marked in bold black letters as a REQUEST FOR SPECIAL PROTOCOL ASSESSMENT. It also should be clearly marked as a carcinogenicity study protocol.

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[3] The Agency published a draft guidance on *Special Protocol Assessment* in February 2000. Once finalized, that guidance will reflect the Agency's current views on submitting information to CDER for special protocol assessment.

[4] Toxicity, Dose-Limiting PD Effects, Exposures 25 times human AUC, Saturation of Absorption, Maximum Feasible Dose (MFD), or Limit Dose.

PDUFA goals for special protocol assessment do not apply to requests for assessment of ongoing carcinogenicity studies. CDER intends to review the protocols for these ongoing studies and to provide a response to such review requests in a timely manner.

A. Information Important to Facilitate Protocol Review

The type of information important for evaluating carcinogenicity protocols will vary with the proposed study design and test approach (see the table at the end of this guidance). In all cases, however, the comprehensive submission of the following information will facilitate the Agency's protocol review. As explained in ICH guidance *S1C,* sponsors should include the basis for dose selection.

1. A toxicology study report should be included reflecting the same conditions as proposed for the carcinogenicity study (same mode of administration, same diet, same rodent strain). The usual duration of this type of study is 90 days if it is intended to support dose selection for a standard 2-year carcinogen bioassay. [5] Studies of shorter duration may be appropriate for alternative bioassays (see the recommendations in ICH *S1B* and *S1C*).

2. Metabolic profiles should be provided for the drug in humans and in the species employed for assessment of carcinogenic potential. [6]

3. Toxicokinetic data should be provided that are sufficient to estimate steady state Cmax and $AUC_{(0\text{-}24)}$ for the parent drug and each major human metabolite at doses employed in the rangefinding study. Data (point estimates as well as individual animal values) should be reported separately for males and females from the same strain as proposed for the bioassay. [7]

4. Exposure (steady state Cmax and $AUC_{(0\text{-}24)}$) data should be provided for the parent drug and for the major metabolites from clinical trials conducted at the maximum recommended human dose (MRHD) or other appropriate human reference dose if the MHRD exposure data are unavailable. [8] Data (point

[5] Irrespective of method of dosage qualification, a rangefinding study is important to ensure that doses selected are likely to be tolerated in the carcinogen bioassay. The need for a rangefinding study may be obviated by the existence of other information, such as chronic toxicity data, depending on the design and outcome of the chronic toxicity studies.

[6] Regardless of endpoint used for dose selection, this information is used to ensure that the animal species proposed for testing is a reasonable surrogate for assessing carcinogenic potential in humans.

[7] This information is needed to justify selected doses on the basis of multiple of human systemic exposure, saturation of absorption, or limit dose endpoints. Irrespective of dose-selection endpoint, this information may assist in the selection of the appropriate dose spread and may be used for product labeling.

[8] In some cases the MRHD may be unknown at the time of carcinogenicity protocol initiation, and an alternative reference dose may be used to determine human exposure. An example of an acceptable alternative approach could

estimates as well as individual values) should be reported separately for males and females.

5. Plasma protein binding data should be provided for the parent drug and the major human metabolites (to the extent feasible) in the rodent test species over the range of concentrations encountered in the dose-rangefinding experiment and in humans at concentrations encountered in clinical trials conducted at the reference dose.

6. A summary of the investigations into the genotoxic potential of the drug and its major human metabolites should be included.[9]

B. The Resubmission of Previously Submitted Reports

When a sponsor relies on reports critical to the chosen dose-selection endpoint that were previously submitted to the Agency, CDER encourages sponsors to resubmit the actual reports or, at least, summaries of the reports. Previously submitted reports can be referenced by submission number and correspondence date (rather than being resubmitted), but submitting the actual reports or their summaries will speed the Agency's review of the carcinogenicity protocol.

C. Use of Body Weight Gain Decrements in a Range Finding Study in Establishing Top Dose

In a dietary administration study, when body weight gain decrements are accompanied by reductions in food consumption and such body weight effects are the only basis for dosage selection, it is important for the sponsor to document that the reduced consumption is not a consequence of a palatability problem. This documentation is important because if the drug is not palatable, higher doses might be tolerated with another mode of administration (e.g., gavage), and the proposed dietary mode of administering doses may not be appropriate.

D. The Selection of Doses for Rangefinding Experiments

The chosen doses should clearly elicit effects that can be used as endpoints as recommended in the ICH guidances. The doses selected should include a dose that is without significant toxicity. It is generally unnecessary to include the maximum feasible dose in the design of the rangefinding experiments when it is known that doses lower than the maximum feasible dose, when administered by the same mode of administration in other dose selection studies, are clearly not tolerated or exceed other acceptable dose selection endpoints. In the absence of such information from other studies, it may be prudent to include the maximum feasible dose in the design of the rangefinding experiments.

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be to determine exposure at a human dose eliciting toxicity such that higher doses would not be acceptable for the indication. The basis for the choice of the human dose used in the comparison should be provided.

[9] This information is used to develop the multiple of human systemic exposure and limit dose endpoints.

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159 **E. Presentation of Data from Rangefinding or Other Toxicity Studies**
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161 Results of toxicity studies submitted in support of dose-selection should be presented in a
162 tabular format and reported separately for males and females. Histopathology tables that
163 provide information on both incidence and severity of findings are important to allow
164 adequate dose selection. Clinical pathology tables should include the group mean value
165 and range for each parameter reported. Graphical illustration of changes in body weight
166 over the course of the study is encouraged.
167
168 **F. Use of the Limit Dose**
169
170 The ICH guidance *S1C(R)* supports the use of a limit dose (1500 mg/kg/day) when
171 certain criteria are met. One of those criteria is that it can be ensured that the rodent
172 exposure to the drug and metabolites at 1500 mg/kg/day exceeds systemic human
173 exposure (AUC) at the MRHD by greater than an order of magnitude. For the purposes
174 of this guidance, CDER considers this has been demonstrated if the lower 95 percent
175 confidence limit for AUC in the rodent is at least 10 times the AUC in humans at the
176 MRHD.
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Table: The Types of Data Useful for Evaluation of Carcinogenicity Bioassay Protocols

Dose Selection Endpoint	Types of Data Useful for Evaluation of Carcinogenicity Bioassay Protocols					
	General Toxicity Information	Genotoxicity	Animal Metabolism	Animal AUC (Unbound)	Human Metabolism	Human AUC (Unbound)
Toxicity (MTD)	√	a	m	---	m	---
Multiple of Human Exposure (25 X)	√	√	√	√	√	√
Saturation of Absorption of Drug Related Substances	√	a	√	√	√	√
MFD	√	a	m	---	m	---
Limit Dose	√	√	√	√	√	√
Pharmacodynamic Effects	√	a	m	---	m	---

√ Important to support this dose selection endpoint for alternative and standard model
a Important for selection of alternative model for these dose selection endpoints
m Information used primarily to support test model (species and strain) for these endpoints
--- Not essential